

## **Remarks**

This REPLY is in response to an Office Action mailed September 11, 2006. A Petition for Extension of Time and the appropriate fee accompany this REPLY. The numbering of sections of this REPLY below are the same as in the Office Action.

### **1. Declaration**

The Examiner objected to the Declaration as defective “because: the specification to which the oath or declaration is directed has not been adequately identified.” Office Action, page 2. The Examiner did not point out with particularity what identifying features of the Declaration were defective. Applicants would appreciate clarification if necessary in light of the remarks below.

Applicants respectfully submit that this objection is improper. Applicants draw the Examiner’s attention to the Declaration filed on August 12, 2004. That Declaration includes a caption with the application number, filing date, title and names of the Inventors signing the Declaration. In the body of the Declaration, the Inventors stated: “the specification of which ... was filed with the above-identified ‘Filed’ date and ‘Appln. No.’” Applicants respectfully submit that this “incorporation by reference” is a valid incorporation for purposes of this Declaration and that the Declaration is not defective and request that the Declaration be accepted..

Applicants note that the spelling of Xiaolan Chen was corrected on the face of the Declaration with the inventor’s initials and the date of the change indicated as August 4, 2004. Applicants note that the signature date of the Declaration is August 4, 2004, so the change to the Declaration did not occur “after signing” the Declaration and thus does not render the Declaration defective.

### **2-3. Claim Rejections Under 35 U.S.C. §102**

Claims 1-4 stand rejected under 35 U.S.C. §102(e) as anticipated by Wang et al (US 2004/0142896 A1; the ‘896 publication). In particular, the Examiner referred to paragraph [0078] of the ‘896 publication as anticipating the instant claims.

In response, Applicants point out that there are only three inventors of the ‘896 publication, Jui H. Wang, Long Shen and Xiaolan Chen. Applicants note that the same three inventors are also named in the instant application. Thus, Applicants submit that the invention of the subject matter of the [0078] is not “by another” and therefore that the ‘896 publication is not applicable under 35 U.S.C. §102(e) against the instant claims.

#### 4-5. Claim Rejections Under 35 U.S.C. §103

Claims 1-22 stand rejected under 35 U.S.C. §103(a) as being obvious over Wang et al. (US Patent 6,291,438; the “438” patent) and Wang et al (US Patent No: 5,858,988, the “988” patent) in view of Hammond et al and Parrish et al.

Applicants respectfully disagree for at least the following reasons. As explained further below, the prior art does not teach or suggest the modifications to siRNA as claimed without undue experimentation and with a reasonable likelihood of success. First, the Examiner noted: “Wang ‘438 and ‘988 does not teach the modification of short interfering RNA (siRNA), or the use of siRNA in a therapeutic method.” Office Action, page 5. Second, Hammond teaches highly variable effects of siRNA and points to the uncertainties of its use and therefore does not provide a teaching sufficient for a person of ordinary skill to arrive at Applicants’ claimed invention “without undue experimentation and with a reasonable likelihood of success.” Moreover, Parrish teaches highly variable effects of modifications of RNAs and teaches away from Applicants’ invention. Finally, Applicants’ results are totally unexpected based on the prior art.

#### Hammond

Hammond is a review article that presents a summary of some of the work on siRNA done in worms (*C. elegans*), with some speculation about potential applications of siRNA to other organisms. Unfortunately, the “BEST COPY AVAILABLE” provided by the Examiner is very difficult to read, and no page numbers are readable. Applicants would appreciate a more readable copy of Hammond. Applicants acknowledge the Examiner’s comment: “Hammond et al. do not teach use of siRNAs.” Office Action, page 6. Applicants provide the following remarks.

First, Applicants submit that the teachings of Hammond represent at best an “invitation to experiment.” The field of siRNA (or RNAi) is very new, and the efficacy or value of siRNA was, at the time Hammond was published, in some doubt. Specifically, Hammond points out the speculative nature of wider use of siRNA beyond the tantalizing early findings in worms:

The use of RNAi as a method to alter gene expression has been attempted in a wide variety of organisms, using different methods (BOX 3) and with varying degrees of success (TABLE 1). ... *Xenopus* and mouse, has been shown to have some capacity for RNAi; however, there seem to be significant limitations. ... Unfortunately, the use of this approach is, at present, limited to a narrow developmental window, and effects provoked in early embryos do not persist after implantation. [emphasis added.]

Based on the speculative nature of Hammond, Applicants submit that the disclosure in Hammond is at best, an “invitation to experiment” and may render Applicants’ derivatized siRNA “obvious to try” but

does not represent a teaching or suggestion to a person of ordinary skill in the art to achieve the claimed effects “without undue experimentation with a reasonable likelihood of success” as required under the current law of obviousness under 35 U.S.C. §103. Applicants therefore respectfully request the Examiner to reconsider the rejections and find the claims patentable.

### **Parrish**

The Examiner stated: “Parrish et al. teach that some common nucleotide modifications, including phosphorothioate, sugar modifications, and terminal cap structures are well tolerated in interfering RNAs.” Office Action, page 6.

As with Hammond discussed above, the “BEST COPY AVAILABLE” is not clear and Applicants request the Examiner to provide a more readable copy of Parrish. Nonetheless, in the interest of moving this application forward, Applicants present the following remarks about Parrish.

First, there is no disclosure, teaching or suggestion to modify an siRNA by derivatizing it with DNP or any other group as claimed. Second, although Parrish discloses several types of modifications to RNA molecules (e.g., Figure 5), Applicants submit that Parrish actually teaches away from Applicants’ invention as claimed. A reading of Parrish (Figure 5) reveals that the results obtained are highly variable, with effects ranging from “+++” (no change from unmodified siRNA, to “-” (no effect). Thus, even considering the modifications specifically pointed out, some modifications (4 of 16 or 25%) **abolished** siRNA activity completely, many (7 of 16 or 44%) had intermediate efficacy, and some other (5 of 16 or 31%) retained the activity of underderivatized siRNA. Thus, according to Figure 5, 11 of 16 (more than 2/3) of the modified siRNAs had **decreased activity** compared to underderivatized siRNA. Importantly, **none** of the derivatized siRNAs in Parrish showed **any increase** in activity compared to underderivatized siRNA. Nothing in Parrish teaches or suggests that derivatizing siRNA would **improve** gene silencing as Applicants have disclosed. Rather, Applicants submit that Parrish would be a disincentive for one to attempt to provide siRNAs with improved efficacy compared to underderivatized siRNAs.

Applicants therefore submit that either: (1) results of Parrish are unpredictable, and the “teaching” is, at best, an “invitation to experiment” or “obvious to try,” or (2) that Parrish actually teaches away from Applicants’ invention as claimed.

In contrast with the cited art described above, Applicants demonstrated that poly-DNP siRNA substantially **increased activity** above that found with underderivatized siRNA. Thus, Applicants’ results were totally unexpected based on the teachings of the ‘438, ‘998 patents, Hammond and Parrish, either alone or in any combination.

#### **6-7. Double Patenting**

Claim 1 stands provisionally rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claim 1 of co-pending Application No. 11/294,693 (the “‘693” publication).

Applicants point out that the instant application has a priority date of March 13, 2003 and a filing date of March 15, 2004. The ‘693 publication has a priority date of November 22, 2004 and a filing date of November 22, 2005. Thus, the instant application is the “earlier-filed application” under MPEP §804, whether considered based on the filing dates or on the priority dates.

Thus, in light of the Applicants’ remarks herein, and the lack of proper rejections under 35 U.S.C. §102(e) or §103(a) as described above, the only remaining rejection is the non-statutory double patenting rejection.

According to the MPEP §804 II(B)(1):

If a “provisional” non-statutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Additionally,

If “provisional” ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer.

Applicants therefore submit that this double patenting rejection is improper and should be withdrawn.

#### **8. Double Patenting**

Claims 1-22 stand rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-48 of US Patent 6,291,438 or claims 1-63 of US Patent No. 5,858,988 in view of Hammond et al. And Parrish et al. Office Action, page 7.

According to MPEP§804(B)(1):

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim. [emphasis added.]

Applicants respectfully submit that this rejection is not proper. Neither Hammond nor Parrish is a patent and there are no claims over which the instant claims can be alleged to be "double." Moreover, as the Examiner noted: "However, Wang '438 and '099 does not teach the modification of short interfering RNA (siRNA), or the use of siRNA in a therapeutic method" Office Action, page 5. Finally, as described above, the instant claims are not anticipated by and are not obvious over the cited art. In particular, the combination of either or both Wang patents and Hammond and Parrish cannot form the basis for a valid rejection under 35 U.S.C. §103(a) because Hammond is speculative and Parrish teaches away from Applicants' invention as claimed. The arguments presented above regarding the §103 rejection are herein incorporated by reference.

Therefore, Applicants respectfully submit that there is no basis for any double patenting rejection over the references cited.

### Conclusion

Applicants respectfully submit that all of the stated grounds for rejection of claims 1-22 are either improper or are overcome, and Applicants request the Examiner to reconsider the rejections and find the claims allowable. Applicants further request the Examiner to issue a Notice of Allowance.

The Examiner is invited to make contact with the undersigned if she believes that a conversation would move the application forward.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-4089 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

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